Cerebral Aneurysm Associated with Multiple Endocrine Neoplasia, Type 1

—Case Report—

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Abstract

Cerebral aneurysm associated with pituitary adenoma and other endocrine dysfunctions occurred in a 45-year-old female suffering from multiple endocrine neoplasia, type 1 (Wermer's syndrome). She died of subarachnoid hemorrhage secondary to rupture of the aneurysm. Pituitary adenoma and/or other endocrine dysfunctions associated with multiple endocrine neoplasia, type 1 may be a factor in the aneurysm formation.

Key words: cerebral aneurysm, pituitary tumor, endocrine dysfunction, hyperparathyroidism, subarachnoid hemorrhage

Introduction

Multiple endocrine neoplasia, type 1 (MEN-1), Wermer's syndrome, is a rare endocrine disorder involving the pituitary gland, parathyroid glands, pancreatic islet cells, and other endocrine glands.

The association of cerebral aneurysm and MEN-1 has not previously been reported, despite the known association of pituitary adenoma, a manifestation of MEN-1, and cerebral aneurysms.^{3,5,8,9,11-13} Skull base deformities caused by hyperparathyroidism associated with MEN-1 may also contribute to aneurysm formation because of the resulting mechanical regional circulatory derangements. We report a patient with MEN-1 and a cerebral aneurysm, and discuss the various endocrinopathies that may cause aneurysm formation.

Case Report

A 45-year-old female was admitted to our hospital on January 20, 1988 with a chief complaint of mild right hemicrania persisting for 6 months. Headache was temporarily relieved by ipsilateral superficial tem-

poral artery compression. Physical examination revealed an obese, mentally retarded female with pigeon chest, scoliosis to the left, short neck, and micrognathia. Neurological examination found no abnormalities. Amenorrhea had occurred for the past 6 months, and she also had a history of multiple long bone fractures. Her family history had no migraine headaches, mental retardation, bone diseases, peptic ulcers, endocrine disorders, and hypertension.

Postcontrast computed tomographic (CT) scans of the brain on admission revealed a large unruptured saccular aneurysm approximately 20 mm in diameter (Fig. 1 *left*). Cerebral angiograms were not possible because of hemorrhagic diathesis. Plain x-ray films of the skull demonstrated a thickened and napped cranial vault with diffusely decreased bone density. The skull base was deformed and flattened with platybasia. Other bones also showed signs of demineralization and subperiosteal resorption. Some long bones had deformities with evidence of healed fractures.

Laboratory studies of blood and urine samples disclosed hypercalcemia (5.8 mEq/l, normal 4.5-5.5 mEq/l) and hypophosphatemia (2.1 mg/dl, normal 3-4.5 mg/dl) with increased urine calcium excretion

Fig. 1 *left*: Postcontrast CT scan, showing a unruptured cerebral aneurysm about 20 mm in diameter in the suprasellar cistern. *right*: CT scan just after onset of subarachnoid hemorrhage, showing the subarachnoid space filled with blood and the negative shadow of the aneurysm.

(273 mg/day, normal 135–250 mg/day), indicating hyperparathyroidism. The tubular reabsorption of phosphate was slightly decreased at 79.4% (normal 85–98%), and serum C-terminal parathyroid hormone and urine free hydroxyproline levels were elevated at 9.2 ng/ml (normal 0.15–1.2 ng/ml) and 3.35 mg/day (normal <2.5 mg/day), respectively.

Endocrine hormone testing showed a high prolactin level (100 ng/ml, normal <20 ng/ml) and hyperreaction to thyrotropin-releasing hormone, strongly suggesting that the amenorrhea was secondary to a prolactin-producing adenoma of the pituitary gland. Interestingly, the CT scans and plain x-ray films of the skull showed no pituitary mass. Other significant laboratory data included fasting hypergastrinemia (2500 pg/ml, normal <50 pg/ml) and normal insulin level (12 μ U/ml). Based on these observations, the diagnosis was MEN-1.

She suffered a massive subarachnoid hemorrhage due to rupture of the aneurysm on February 8, 1988 (Fig. 1 *right*), and died 7 days later. Postmortem examination revealed that the brain was markedly edematous and softened, consistent with prolonged mechanical ventilation. The skull was diffusely thickened and the base of the skull was flattened with platybasia. The ruptured cerebral aneurysm originated from the anterior communicating artery.

Histological examination revealed no evidence of fibromuscular dysplasia or medial cystic necrosis of the aneurysm or adjacent vasculature. The intracranial cerebral arteries also showed no evidence of atherosclerosis. The pituitary gland adenoma was found (Fig. 2 *upper*), although the sella turcica was

Fig. 2 Photomicrographs of endocrine organs. *upper*: Pituitary microadenoma completely necrosed because of prolonged mechanical ventilation. Azan-Mallory stain, $\times 60$. *middle*: Chief cell adenoma of parathyroid gland. HE stain, $\times 30$. *lower*: Pancreatic islet cell hyperplasia with mitotic figures (*arrow*). HE stain, $\times 120$.

not enlarged. However, due to massive edema and tissue necrosis, we could not identify the specific hormone-secreting cell type. Two parathyroid adenomas, one 50 $\times$ 40 $\times$ 30 mm and the other 5 $\times$ 5 $\times$ 5 mm, were also detected (Fig. 2 *middle*). The long bones showed evidence of osteitis fibrosa cystica. There was pancreatic islet cell hyperplasia with some cellular pleomorphism and mitotic figures (Fig. 2 *lower*), but no unequivocal islet cell tumor

was found. Immunohistochemical studies utilizing a gastrin antibody (PAP kit, K516; DAKO Corp., Santa Barbara, Cal., U.S.A.) revealed widespread gastrin-positive cells in the antrum and fundus of the stomach, but no ulcer in the stomach or duodenum. Further histological findings indicated that MEN-1 included cortical adenoma of the adrenal glands, adenomatous goiter of the thyroid gland, mammary duct papillomatosis, and fibroma and Brenner's tumor of the ovaries. This wide range of findings confirmed the diagnosis of MEN-1.^{1,7,14)}

Discussion

MEN-1 is a rare endocrine syndrome with an estimated incidence of 0.02–0.2 per thousand.⁷⁾ MEN-1 is transmitted in an autosomal dominant mode without generation skip. However, family history is positive in only 50% of cases. Pituitary adenoma is present in 50–60% of MEN-1 patients and two-thirds of these tumors are prolactinomas.^{1,7)}

Cerebral aneurysm occurs in approximately 7% of patients with pituitary adenoma.^{5,13)} Several hypotheses have been proposed to explain this interesting and high incidence including mechanical compression⁵⁾ or invasion⁹⁾ of the regional arteries by the pituitary tumor, and hemodynamic changes in regional vessels near the pituitary adenoma.¹¹⁾ In our case, the relatively small size of the pituitary tumor with no invasion suggests that the skull base deformities secondary to the hyperparathyroidism associated with MEN-1 may have caused the aneurysm formation as a result of mechanical and/or hemodynamic derangements of the regional circulation. Although the exact cause and morphogenesis of the cerebral aneurysm remain speculative in this case, pituitary adenoma and/or other endocrine dysfunctions associated with MEN-1 may be a factor in aneurysm formation as previously suggested.^{4,6,13)} The possibility of simultaneous occult cerebral aneurysm in patients with pituitary adenoma and/or other endocrinopathies should be considered.

Endocrine dysfunction may induce fibromuscular dysplasia of arterial walls, causing cerebral aneurysm formation.^{4,6)} Furthermore, patients with MEN-1 associated with Marfan-like syndrome¹⁰⁾ or von Recklinghausen's disease²⁾ may have vascular abnormalities, including medial necrosis of the arterial walls which can also contribute to cerebral aneurysm formation. However, these abnormalities were not detected in our case. Further studies are needed to evaluate the above hypotheses for the etiology of aneurysm formation in patients with pituitary adenoma and other endocrinopathies.

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